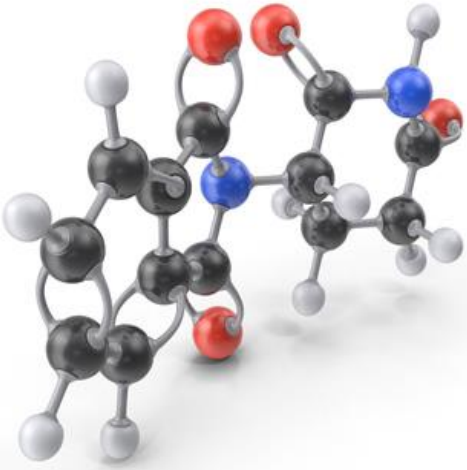

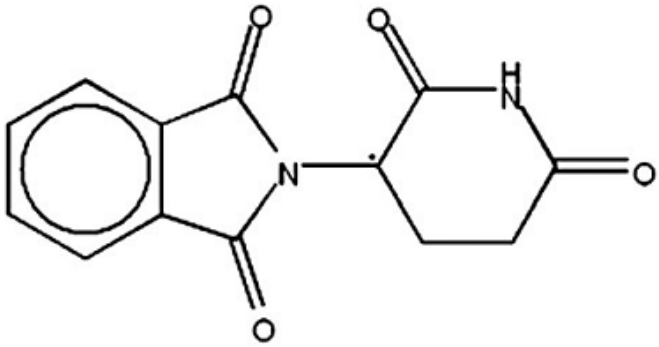

Thalidomide

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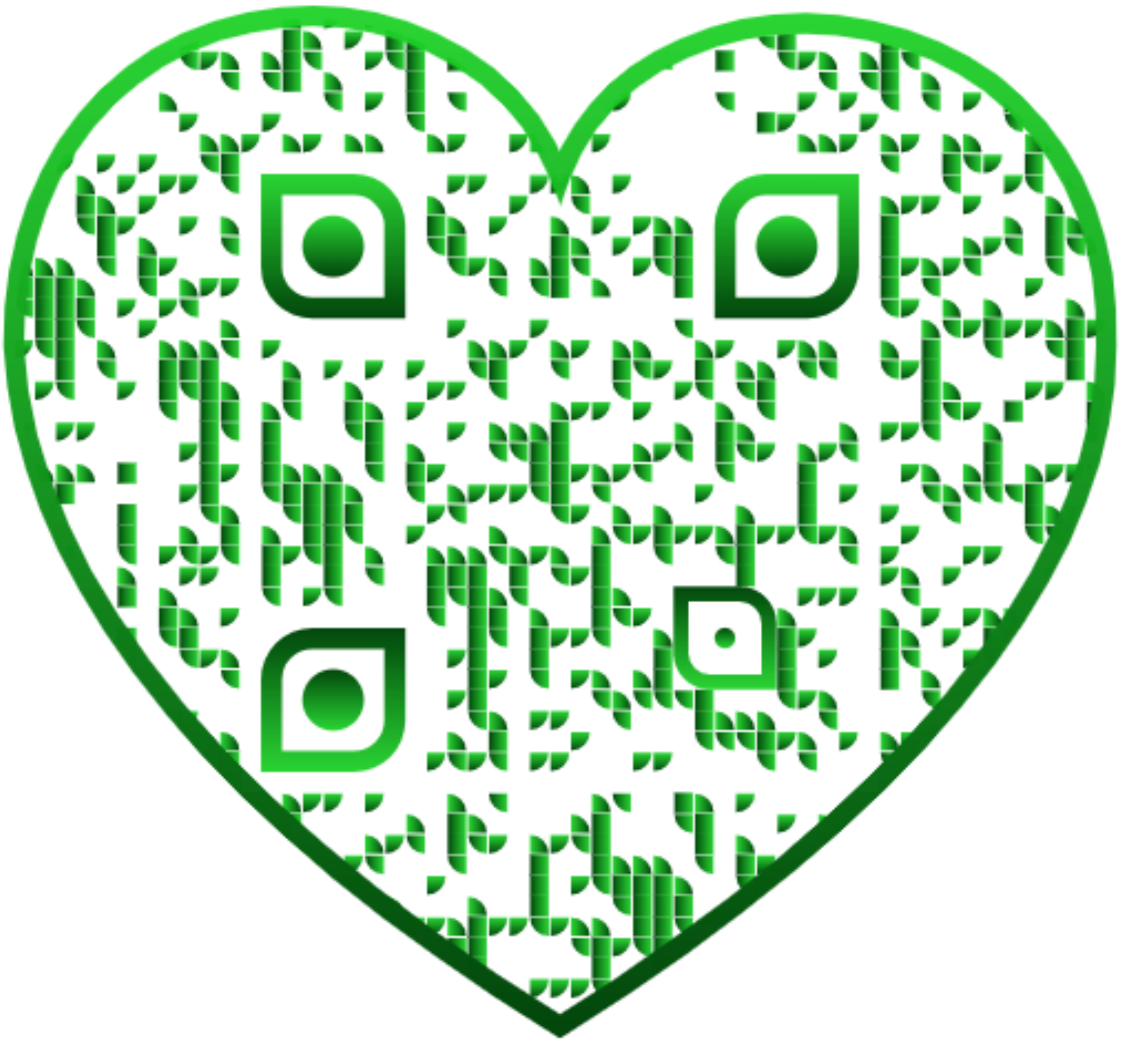
The Important Thing
Is To Never Stop Questioning
MMO

Designed by: MMO_team



Abstract: Thalidomide was a widely used drug in the late 1950s and early 1960s for the treatment of nausea in pregnant women. It became apparent in the 1960s that Thalidomide treatment resulted in severe birth defects in thousands of children. Though the use of Thalidomide was banned in most countries at that time, Thalidomide proved to be a useful treatment for leprosy and later, multiple myeloma. In rural areas of the world that lack extensive medical surveillance initiatives, Thalidomide treatment of pregnant women with leprosy has continued to cause malformations. Research on Thalidomide mechanisms of action is leading to a better understanding of molecular targets. With an improved understanding of these molecular targets, safer drugs may be designed. The Thalidomide tragedy marked a turning point in toxicity testing, as it prompted United States and international regulatory agencies to develop systematic toxicity testing protocols; the use of Thalidomide as a tool in developmental biology led to important discoveries in the biochemical pathways of limb development. In celebration of the Society of Toxicology's 50th Anniversary, which coincides with the 50th anniversary of the withdrawal of Thalidomide from the market, it is appropriate to revisit the lessons learned from the Thalidomide tragedy of the 1960s.

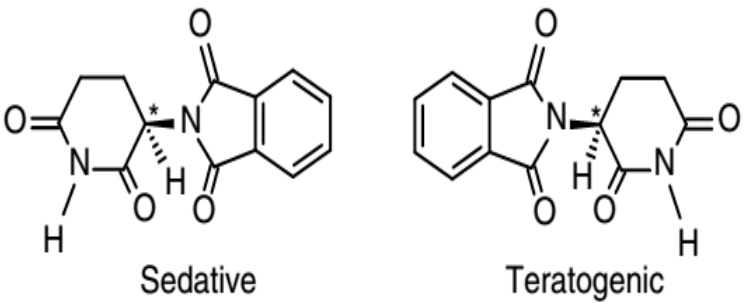
INTRODUCTION

- What Thalidomide is?

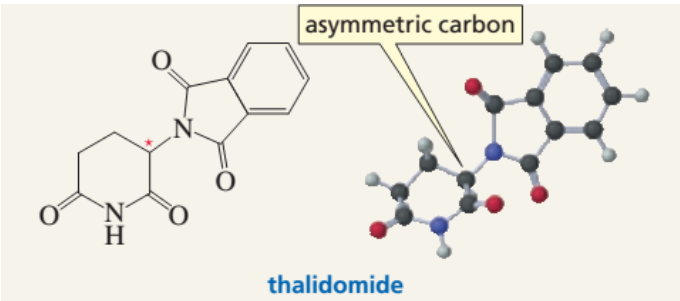
Thalidomide is an oral, small-molecule immunomodulatory drug, an agent that can modify or regulate the immune system. It has both anti-inflammatory and anti-cancer activities. immunomodulatory drugs induce immune responses, enhance the activity of immune cells, and inhibit inflammation by altering the levels of growth factors called cytokines and interleukins. immunomodulatory drugs kill cancer cells by enhancing the activation of (T-cell), and by inhibiting the growth of blood vessels upon which cancer cells depend for sustenance and growth.

STRUCURE OF THALIDOMIDE

It was found that Thalidomide molecule can exist in two stereoisomeric forms, one form is active as sedative but the other is responsible for its teratogenic activity (harmful effects on fetus).



Thalidomide stereoisomers



The dextrorotatory isomer has stronger sedative properties, but the commercial drug was a racemic mixture. However, it wasn't recognized that the levorotatory isomer was highly teratogenic—it causes horrible birth defects—until it was noticed that women who were given the drug during the first three months of pregnancy gave birth to babies with a wide variety of defects, such as deformed limbs. It was eventually determined that the dextrorotatory isomer also has mild teratogenic activity and that both enantiomers racemize in vivo. Thus, it is not clear whether giving those women only the dextrorotatory isomer would have decreased the severity of the birth defects. Thalidomide recently has been approved—with restrictions—to treat leprosy as well as melanomas.

THERAPEUTIC USES OF THLIDOMIDE

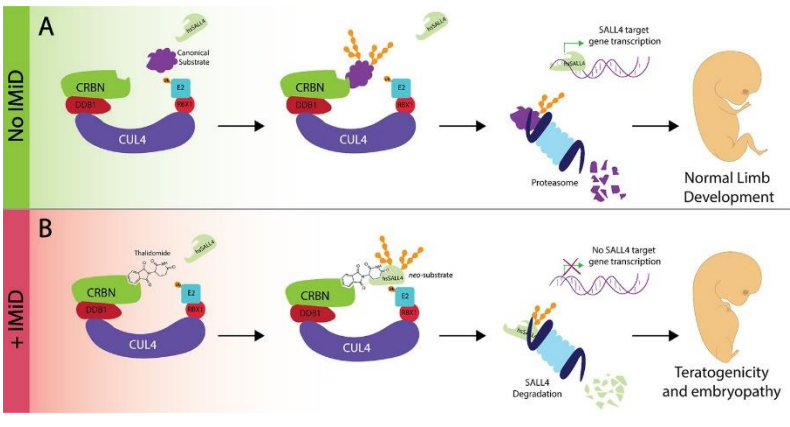
1) From 1957 to 1966, it was prescribed to pregnant women outside the US to combat symptoms associated with morning sickness.

2) In 1998, it was first approved in the US for the treatment of erythema nodosum leprosum (ENL), an inflammatory condition seen in some patients with leprosy.

3) In 2006, it was approved by the FDA for the treatment of myeloma in combination with other agents, such as dexamethasone.

THALIDOMIDE MECHANISM OF ACTION

- After taking Thalidomide orally, it goes normally to the site of effect after getting metabolized. Just here body differentiate between them. Thalidomide normally binds to TBX5 DNA binding domain. There are various amino acids found there which are responsible for producing proteins do the action. If Thalidomide is (R) all the amino acids in TBX5 DNA will bind normally including (alpha Arginine in position 81) and thus the required action is achieved.
- However, if Thalidomide doesn't fit or in another word, (alpha Arginine in position 81) couldn't fit, another mechanism occurs.
- In pregnancy, Thalidomide(S) travels through circulatory system until it reaches placenta. There are one protein and two transcription factors in the embryo that are essential in limbs growing. Cereblon, SALL4, and P63 those are target of free thalidomide. Cereblon, SALL4 (A & B) , and P63, are different in their original state that can not fit together.
- Thalidomide(S) can bind to Cereblon that forms a complex called (Thalidomide–celebron complex) this one can go and identify SALL4 and P63 transcription factors that are responsible for pxtermities growing. They all can bind together and produced a complex consist of DDB1 (DNA-Damage-binding) ROC1 (Ring finger protein) CUL4 (Cullin) this complex is a protein that change the structure of P63 and SALL4 resulting in wrong transcription and deformities in limbs, and other defects.



SIDE EFFECTS OF THALIDOMIDE

- Harmful effects on fetus.
- kidney malformations.
- ventricular septal defects.
- dental malformations, autism and mental retardation, ocular anomalies, and Duane syndrome (lack of the sixth nerve and aberrant innervation of ocular muscles by the third cranial nerve).

IN CONCLUSION

Because Thalidomide is useful in the treatment of serious diseases, it is likely that this product will continue to be used in therapeutics until safer alternatives become available. Prevention of inadvertent exposure of pregnant women to this drug is a continuing challenge, particularly in parts of the world where access to the drug is less restricted than in the United States. The development of Thalidomide analogs that retain the therapeutic benefits of the drug without its teratogenic liability is a second challenge. The goal of a safe Thalidomide analog may be elusive if the therapeutic mechanisms of action and the teratogenic mechanisms of action are closely related or even identical.

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